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   * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

 FILE 'HOME' ENTERED AT 10:23:52 ON 19 NOV 2002

 => fil .bec,canc
 COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                            ENTRY    SESSION
 FULL ESTIMATED COST                                         0.21       0.21

 FILES 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS, NTIS,
       ESBIOBASE, BIOTECHNO, WPIDS, CANCERLIT' ENTERED AT 10:24:38 ON 19 NOV 2002
 ALL COPYRIGHTS AND RESTRICTIONS APPLY.  SEE HELP USAGETERMS FOR DETAILS.

 12 FILES IN THE FILE LIST

 => s (matrix or ecm)(5a)(metalloprote?)
 FILE 'MEDLINE'
          95678 MATRIX
           4374 ECM
          16855 METALLOPROTE?
 L1        7690 (MATRIX OR ECM)(5A)(METALLOPROTE?)

 FILE 'SCISEARCH'
         246062 MATRIX
           4652 ECM
          17635 METALLOPROTE?
 L2       10398 (MATRIX OR ECM)(5A)(METALLOPROTE?)

 FILE 'LIFESCI'
          24827 MATRIX
           1161 ECM
           3384 METALLOPROTE?
 L3        1384 (MATRIX OR ECM)(5A)(METALLOPROTE?)

 FILE 'BIOTECHDS'
           4481 MATRIX
             32 ECM
            190 METALLOPROTE?
 L4           42 (MATRIX OR ECM)(5A)(METALLOPROTE?)

 FILE 'BIOSIS'
         114684 MATRIX
           4734 ECM
          18905 METALLOPROTE?
 L5       11158 (MATRIX OR ECM)(5A)(METALLOPROTE?)

 FILE 'EMBASE'
          86400 MATRIX
           3878 ECM
          14558 METALLOPROTE?
 L6        7727 (MATRIX OR ECM)(5A)(METALLOPROTE?)

 FILE 'HCAPLUS'
         376926 MATRIX
           4441 ECM
          17053 METALLOPROTE?
 L7        8770 (MATRIX OR ECM)(5A)(METALLOPROTE?)

 FILE 'NTIS'
          43570 MATRIX
            472 ECM
            185 METALLOPROTE?
 L8           91 (MATRIX OR ECM)(5A)(METALLOPROTE?)
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FILE 'ESBIOBASE'
         41126 MATRIX
          2198 ECM
          7644 METALLOPROTE?
L9         4822 (MATRIX OR ECM)(5A)(METALLOPROTE?)

FILE 'BIOTECHNO'
         32004 MATRIX
          1599 ECM
          7330 METALLOPROTE?
L10        3791 (MATRIX OR ECM)(5A)(METALLOPROTE?)

FILE 'WPIDS'
        121264 MATRIX
           500 ECM
          1321 METALLOPROTE?
L11         846 (MATRIX OR ECM)(5A)(METALLOPROTE?)

FILE 'CANCERLIT'
         25579 MATRIX
          1739 ECM
          6186 METALLOPROTE?
L12        4019 (MATRIX OR ECM)(5A)(METALLOPROTE?)

TOTAL FOR ALL FILES
L13       60738 (MATRIX OR ECM)(5A)(METALLOPROTE?)

=> s l13(10a)(membrane# or transmembrane#)
FILE 'MEDLINE'
        590216 MEMBRANE#
         36224 TRANSMEMBRANE#
L14        822 L1 (10A)(MEMBRANE# OR TRANSMEMBRANE#)

FILE 'SCISEARCH'
        440609 MEMBRANE#
         35430 TRANSMEMBRANE#
L15        729 L2 (10A)(MEMBRANE# OR TRANSMEMBRANE#)

FILE 'LIFESCI'
        147518 MEMBRANE#
         15890 TRANSMEMBRANE#
L16        111 L3 (10A)(MEMBRANE# OR TRANSMEMBRANE#)

FILE 'BIOTECHDS'
         16367 MEMBRANE#
          1661 TRANSMEMBRANE#
L17          2 L4 (10A)(MEMBRANE# OR TRANSMEMBRANE#)

FILE 'BIOSIS'
        794115 MEMBRANE#
         41258 TRANSMEMBRANE#
L18        871 L5 (10A)(MEMBRANE# OR TRANSMEMBRANE#)

FILE 'EMBASE'
        469143 MEMBRANE#
         32852 TRANSMEMBRANE#
L19        600 L6 (10A)(MEMBRANE# OR TRANSMEMBRANE#)

FILE 'HCAPLUS'
        644329 MEMBRANE#
         41705 TRANSMEMBRANE#
L20        868 L7 (10A)(MEMBRANE# OR TRANSMEMBRANE#)

FILE 'NTIS'
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          14866 MEMBRANE#
            312 TRANSMEMBRANE#
L21          15 L8 (10A)(MEMBRANE# OR TRANSMEMBRANE#)

FILE 'ESBIOBASE'
         192291 MEMBRANE#
          18727 TRANSMEMBRANE#
L22         494 L9 (10A)(MEMBRANE# OR TRANSMEMBRANE#)

FILE 'BIOTECHNO'
         150132 MEMBRANE#
          20149 TRANSMEMBRANE#
L23         416 L10(10A)(MEMBRANE# OR TRANSMEMBRANE#)

FILE 'WPIDS'
         114794 MEMBRANE#
           1449 TRANSMEMBRANE#
L24          31 L11(10A)(MEMBRANE# OR TRANSMEMBRANE#)

FILE 'CANCERLIT'
         105577 MEMBRANE#
           8686 TRANSMEMBRANE#
L25         476 L12(10A)(MEMBRANE# OR TRANSMEMBRANE#)

TOTAL FOR ALL FILES
L26        5435 L13(10A)(MEMBRANE# OR TRANSMEMBRANE#)

=> s l26 not 1996-1999/py
FILE 'MEDLINE'
        1751463 1996-1999/PY
L27         488 L14 NOT 1996-1999/PY

FILE 'SCISEARCH'
        3763098 1996-1999/PY
L28         406 L15 NOT 1996-1999/PY

FILE 'LIFESCI'
         453627 1996-1999/PY
L29          59 L16 NOT 1996-1999/PY

FILE 'BIOTECHDS'
          55748 1996-1999/PY
L30           2 L17 NOT 1996-1999/PY

FILE 'BIOSIS'
        2243480 1996-1999/PY
L31         497 L18 NOT 1996-1999/PY

FILE 'EMBASE'
        1633088 1996-1999/PY
L32         336 L19 NOT 1996-1999/PY

FILE 'HCAPLUS'
        3309514 1996-1999/PY
L33         501 L20 NOT 1996-1999/PY

FILE 'NTIS'
         121911 1996-1999/PY
L34           7 L21 NOT 1996-1999/PY

FILE 'ESBIOBASE'
        1019834 1996-1999/PY
L35         276 L22 NOT 1996-1999/PY
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FILE 'BIOTECHNO'
        440524 1996-1999/PY
L36         225 L23 NOT 1996-1999/PY

FILE 'WPIDS'
       2887589 1996-1999/PY
L37          24 L24 NOT 1996-1999/PY

FILE 'CANCERLIT'
        370160 1996-1999/PY
L38         266 L25 NOT 1996-1999/PY

TOTAL FOR ALL FILES
L39        3087 L26 NOT 1996-1999/PY

=> s l39 not 2000-2002/py
FILE 'MEDLINE'
       1410095 2000-2002/PY
L40          44 L27 NOT 2000-2002/PY

FILE 'SCISEARCH'
       2714461 2000-2002/PY
L41          44 L28 NOT 2000-2002/PY

FILE 'LIFESCI'
        270882 2000-2002/PY
L42          15 L29 NOT 2000-2002/PY

FILE 'BIOTECHDS'
         43376 2000-2002/PY
L43           0 L30 NOT 2000-2002/PY

FILE 'BIOSIS'
       1472035 2000-2002/PY
L44          60 L31 NOT 2000-2002/PY

FILE 'EMBASE'
       1213787 2000-2002/PY
L45          39 L32 NOT 2000-2002/PY

FILE 'HCAPLUS'
       2721177 2000-2002/PY
L46          58 L33 NOT 2000-2002/PY

FILE 'NTIS'
         43068 2000-2002/PY
L47           2 L34 NOT 2000-2002/PY

FILE 'ESBIOBASE'
        782150 2000-2002/PY
L48          21 L35 NOT 2000-2002/PY

FILE 'BIOTECHNO'
        327557 2000-2002/PY
L49          31 L36 NOT 2000-2002/PY

FILE 'WPIDS'
       2429778 2000-2002/PY
L50           0 L37 NOT 2000-2002/PY

FILE 'CANCERLIT'
        259403 2000-2002/PY
L51          32 L38 NOT 2000-2002/PY
```

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TOTAL FOR ALL FILES
L52         346 L39 NOT 2000-2002/PY

=> dup rem l52
PROCESSING COMPLETED FOR L52
L53          111 DUP REM L52 (235 DUPLICATES REMOVED)

=> s l13(10a)gene/q
FILE 'MEDLINE'
L54         538 L1 (10A)GENE/Q

FILE 'SCISEARCH'
L55         552 L2 (10A)GENE/Q

FILE 'LIFESCI'
L56         168 L3 (10A)GENE/Q

FILE 'BIOTECHDS'
L57          15 L4 (10A)GENE/Q

FILE 'BIOSIS'
L58         784 L5 (10A)GENE/Q

FILE 'EMBASE'
L59         471 L6 (10A)GENE/Q

FILE 'HCAPLUS'
L60        1085 L7 (10A)GENE/Q

FILE 'NTIS'
L61           6 L8 (10A)GENE/Q

FILE 'ESBIOBASE'
L62         363 L9 (10A)GENE/Q

FILE 'BIOTECHNO'
L63         366 L10(10A)GENE/Q

FILE 'WPIDS'
L64          45 L11(10A)GENE/Q

FILE 'CANCERLIT'
L65         292 L12(10A)GENE/Q

TOTAL FOR ALL FILES
L66        4685 L13(10A) GENE/Q

=> s l52 and l66
FILE 'MEDLINE'
L67           7 L40 AND L54

FILE 'SCISEARCH'
L68           6 L41 AND L55

FILE 'LIFESCI'
L69           5 L42 AND L56

FILE 'BIOTECHDS'
L70           0 L43 AND L57

FILE 'BIOSIS'
L71          10 L44 AND L58

FILE 'EMBASE'
```

L72 7 L45 AND L59

FILE 'HCAPLUS'
L73 13 L46 AND L60

FILE 'NTIS'
L74 0 L47 AND L61

FILE 'ESBIOBASE'
L75 7 L48 AND L62

FILE 'BIOTECHNO'
L76 7 L49 AND L63

FILE 'WPIDS'
L77 0 L50 AND L64

FILE 'CANCERLIT'
L78 5 L51 AND L65

TOTAL FOR ALL FILES
L79 67 L52 AND L66

=> dup rem l79
PROCESSING COMPLETED FOR L79
L80 18 DUP REM L79 (49 DUPLICATES REMOVED)

=> d tot

L80 ANSWER 1 OF 18 MEDLINE DUPLICATE 1
TI Identification of the second **membrane**-type **matrix metalloproteinase** (MT-MMP-2) **gene** from a human placenta cDNA library. MT-MMPs form a unique membrane-type subclass in the MMP family.
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (1995 Sep 29) 270 (39) 23013-20.
Journal code: 2985121R. ISSN: 0021-9258.
AU Takino T; Sato H; Shinagawa A; Seiki M
AN 96032735 MEDLINE

L80 ANSWER 2 OF 18 MEDLINE DUPLICATE 2
TI **Membrane**-type **matrix metalloproteinase** (MT-MMP) **gene** is expressed in stromal cells of human colon, breast, and head and neck carcinomas.
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1995 Mar 28) 92 (7) 2730-4.
Journal code: 7505876. ISSN: 0027-8424.
AU Okada A; Bellocq J P; Rouyer N; Chenard M P; Rio M C; Chambon P; Basset P
AN 95224014 MEDLINE

L80 ANSWER 3 OF 18 HCAPLUS COPYRIGHT 2002 ACS
TI MT-MMP
SO Jikken Igaku (1995), 13(15), 1802-4
CODEN: JIIGEF; ISSN: 0288-5514
AU Kinoshita, Takeshi
AN 1995:854429 HCAPLUS
DN 123:333290

L80 ANSWER 4 OF 18 MEDLINE DUPLICATE 3
TI cDNA **sequence** and mRNA tissue distribution of a novel human **matrix metalloproteinase** with a potential **transmembrane** segment.
SO EUROPEAN JOURNAL OF BIOCHEMISTRY, (1995 Aug 1) 231 (3) 602-8.
Journal code: 0107600. ISSN: 0014-2956.
AU Will H; Hinzmann B

AN 95377289 MEDLINE

L80 ANSWER 5 OF 18 MEDLINE DUPLICATE 4
TI Assignment of the human **membrane**-type **matrix metalloproteinase** (MMP14) **gene** to 14q11-q12 by in situ hybridization.
SO GENOMICS, (1995 Jul 20) 28 (2) 360-1.
Journal code: 8800135. ISSN: 0888-7543.
AU Mignon C; Okada A; Mattei M G; Basset P
AN 96015075 MEDLINE

L80 ANSWER 6 OF 18 Elsevier BIOBASE COPYRIGHT 2002 Elsevier Science B.V.
DUPLICATE
AN 1995122271 ESBIOBASE
TI Assignment of the human **membrane**-type **matrix metalloproteinase** (MMP14) **gene** to 14q11-q12 by in situ hybridization
AU Mignon C.; Okada A.; Mattei M.G.; Bassett P.
CS P. Bassett, France.
SO Genomics, (1995), 28/2 (360)
CODEN: GNMCEP ISSN: 0888-7543
DT Journal; Article
LA English

L80 ANSWER 7 OF 18 MEDLINE DUPLICATE 6
TI Cloning of a human **gene** potentially encoding a novel **matrix metalloproteinase** having a C-terminal **transmembrane** domain.
SO GENE, (1995 Apr 3) 155 (2) 293-8.
Journal code: 7706761. ISSN: 0378-1119.
AU Takino T; Sato H; Yamamoto E; Seiki M
AN 95237627 MEDLINE

L80 ANSWER 8 OF 18 HCAPLUS COPYRIGHT 2002 ACS
TI Coordinate regulation of matrix metalloproteases and tissue inhibitor of metalloproteinase expression in human synovial fibroblasts
SO Journal of Rheumatology, Supplement (1995), 43(Osteoarthritis: Challenges for the 21st Century), 123-8
CODEN: JRSUDX; ISSN: 0380-0903
AU DiBattista, John A.; Pelletier, Jean-Pierre; Zafarullah, Muhammad; Fujimoto, Noboru; Obata, Ken'Ichi; Martel-Pelletier, Johanne
AN 1995:532469 HCAPLUS
DN 122:312276

L80 ANSWER 9 OF 18 HCAPLUS COPYRIGHT 2002 ACS
TI Molecular cloning and function of a novel **matrix metalloproteinase** (MMP), **membrane** type-MMP (MT-MMP)
SO Kanazawa Daigaku Juzen Igakkai Zasshi (1995), 104(1), 2-14
CODEN: JUZIAG; ISSN: 0022-7226
AU Takino, Takahisa
AN 1995:784244 HCAPLUS
DN 123:279392

L80 ANSWER 10 OF 18 HCAPLUS COPYRIGHT 2002 ACS
TI Overexpression of metalloproteinase inhibitor in B16F10 cells does not affect extravasation but reduces tumor growth
SO Cancer Research (1994), 54(17), 4791-7
CODEN: CNREA8; ISSN: 0008-5472
AU Koop, Sahadia; Khokha, Rama; Schmidt, Eric E.; MacDonald, Ian C.; Morris, Vincent L.; Chambers, Ann F.; Groom, Alan C.
AN 1994:576418 HCAPLUS
DN 121:176418

L80 ANSWER 11 OF 18 MEDLINE DUPLICATE 7

TI The role of matrix metalloproteases and their inhibitors in tumour invasion, metastasis and angiogenesis.
SO EUROPEAN RESPIRATORY JOURNAL, (1994 Nov) 7 (11) 2062-72. Ref: 124
Journal code: 8803460. ISSN: 0903-1936.
AU Ray J M; Stetler-Stevenson W G
AN 95180397 MEDLINE

L80 ANSWER 12 OF 18 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
TI Cloning of a **gene** encoding a novel **matrix metalloproteinase** with a **transmembrane** structure.
SO Clinical & Experimental Metastasis, (1994) Vol. 12, No. 5, pp. 63.
Meeting Info.: Fifth International Congress of the Metastasis Research Society Bethesda, Maryland, USA September 28-October 1, 1994
ISSN: 0262-0898.
AU Takino, T. (1); Sato, H.; Yamamoto, E.; Seiki, M.
AN 1995:98328 BIOSIS

L80 ANSWER 13 OF 18 MEDLINE DUPLICATE 8
TI A matrix metalloproteinase expressed on the surface of invasive tumour cells.
SO NATURE, (1994 Jul 7) 370 (6484) 61-5.
Journal code: 0410462. ISSN: 0028-0836.
AU Sato H; Takino T; Okada Y; Cao J; Shinagawa A; Yamamoto E; Seiki M
AN 94286011 MEDLINE

L80 ANSWER 14 OF 18 HCAPLUS COPYRIGHT 2002 ACS
TI The role of AP-1 in **matrix metalloproteinase gene** expression
SO Agents and Actions (1993), 39(Spec. Conf. Issue), C215-C218
CODEN: AGACBH; ISSN: 0065-4299
AU Lin, C. W.; Georgescu, H. I.; Evans, C. H.
AN 1994:2136 HCAPLUS
DN 120:2136

L80 ANSWER 15 OF 18 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
TI ASSIGNMENT OF THE HUMAN STROMELYSIN 3 STMY3 GENE TO THE Q11.2 REGION OF CHROMOSOME 22.
SO GENOMICS, (1992) 13 (3), 881-883.
CODEN: GNMCEP. ISSN: 0888-7543.
AU LEVY A; ZUCMAN J; DELATTRE O; MATTEI M-G; RAO M-C; BASSET P
AN 1992:389732 BIOSIS

L80 ANSWER 16 OF 18 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
TI STRUCTURAL CHARACTERIZATION OF MESANGIAL CELL TYPE IV COLLAGENASE AND ENHANCED EXPRESSION IN A MODEL OF IMMUNE COMPLEX-MEDIATED GLOMERULONEPHRITIS.
SO AM J PATHOL, (1992) 141 (1), 85-98.
CODEN: AJPAA4. ISSN: 0002-9440.
AU LOVETT D H; JOHNSON R J; MARTI H-P; MARTIN J; DAVIES M; COUSER W G
AN 1992:410773 BIOSIS

L80 ANSWER 17 OF 18 HCAPLUS COPYRIGHT 2002 ACS
TI Matrix metalloproteinase 2 from human rheumatoid synovial fibroblasts. Purification and activation of the precursor and enzymic properties
SO European Journal of Biochemistry (1990), 194(3), 721-30
CODEN: EJBCAI; ISSN: 0014-2956
AU Okada, Yasunori; Morodomi, Tatsuhisa; Enghild, Jan J.; Suzuki, Ko; Yasui, Atsushi; Nakanishi, Isao; Salvesen, Guy; Nagase, Hideaki
AN 1991:99390 HCAPLUS
DN 114:99390

L80 ANSWER 18 OF 18 HCAPLUS COPYRIGHT 2002 ACS
TI The role of matrix metalloproteinase 3 in the stepwise activation of human rheumatoid synovial procollagenase

SO Biological Chemistry Hoppe-Seyler (1990), 371(Suppl.), 305-10
CODEN: BCHSEI; ISSN: 0177-3593
AU Suzuki, K.; Nagase, H.; Ito, A.; Enghild, J. J.; Salvesen, G.
AN 1990:511462 HCAPLUS
DN 113:111462

=> d ab tot

L80 ANSWER 1 OF 18 MEDLINE DUPLICATE 1
AB **Membrane**-type **matrix metalloproteinase** (MT-MMP), which we have identified recently, is unique in its transmembrane (TM) domain at the C terminus and mediates activation of pro-gelatinase A on the cell surface (Sato, H., Takino, T., Okada, Y., Cao, J., Shinagawa, A., Yamamoto, E., and Seiki, M. (1994) Nature 370, 61-65; Takino, T., Sato, H., Yamamoto, E., and Seiki, M. (1995) Gene (Amst.) 115, 293-298). In addition to MT-MMP, a novel MMP-related cDNA of 2.1 kilobases was isolated from a human placenta cDNA library. The cDNA contains an open reading frame for a new MMP. The deduced protein composed of 604 amino acids was closely related to MT-MMP in the amino acid sequence (66% homology at the catalytic domains) and has a potential TM domain at the C terminus. Monoclonal antibodies raised against the synthetic peptide recognized a 64-kDa protein as the major product in the transfected cells. TIMP-1 fused with the potential TM domain was localized on the cell surface while native TIMP-1 is in the culture medium. Thus, we called the second membrane-type MMP, MT-MMP-2 and renamed MT-MMP, MT-MMP-1. MT-MMP-1 and -2 are thought to form a distinct membrane-type subclass in the MMP family since all the others are secreted as soluble forms. Like MT-MMP-1, expression of MT-MMP-2 induced processing of pro-gelatinase A (68-kDa in gelatin zymography) into the activated form of 62-kDa fragments through a 64-kDa intermediate form. Expression of MT-MMP-2 mRNA was at the highest levels in the brain where MT-MMP-1 was at the lowest level compared to other tissues. MT-MMP-1 and -2 are thought to be utilized for extracellular matrix turnover on the surface of cells under different genetic controls.

L80 ANSWER 2 OF 18 MEDLINE DUPLICATE 2
AB From breast cancer cDNA libraries, we have cloned cDNAs that proved to correspond to the **membrane**-type **matrix metalloproteinase** (MT-MMP) recently identified in human placenta and proposed to be an activator of progelatinase A [Sato, H., Takino, T., Okada, Y., Cao, J., Shinagawa, A., Yamamoto, E. & Seiki, M. (1994) Nature (London) 370, 61-65]. Using one of these cDNAs as a probe, we have detected MT-MMP gene expression in all 83 human carcinoma specimens examined by RNA in situ hybridization and have found MT-MMP transcripts in fibroblastic cells of tumor stroma but not in cancer cells. Comparison with other MMP genes expressed in fibroblastic cells of human carcinomas indicated that the expression pattern of the MT-MMP gene was more closely related to that of the gelatinase A gene than to those of the stromelysin 3 or interstitial collagenase genes. These observations are consistent with the hypothesis that MT-MMP and gelatinase A are cooperating during tumor progression and strengthen the concept that proteolytic activities originating from the stromal component of human carcinomas have a critical role in tumor progression.

L80 ANSWER 3 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AB A review, with 12 refs., on **membrane** type **matrix metalloproteinase** (MT-MMP) possessing activation activity of MMP-2, its **gene** and protein structure as a single MMP possessing trans-membrane domain, and the role in tumor invasion and metastasis by activation of MMP-2.

L80 ANSWER 4 OF 18 MEDLINE DUPLICATE 3
AB The complementary DNA **sequence** of a novel **matrix**

metalloproteinase was isolated from a human lung cDNA library. It consists of 3530 bp and encodes a polypeptide of 669 amino acids. In comparison to other **matrix metalloproteinases**, the deduced **sequence** of the amino acid chain exhibits closest similarity to a recently discovered **membrane**-type **matrix metalloproteinase** of 582 amino acids. Likewise, it is composed of a signal peptide, a prodomain, a catalytic domain, a hemopexin-homologous domain and a C-terminal domain. Furthermore, the novel matrix metalloproteinase shares a similar activation site with its 582-amino-acid homologue, an insertion of eight amino acids in the catalytic domain and a tract of more than 20 hydrophobic amino acids near the C-terminus. The hydrophobic structure in the C-terminal domain suggests that the novel **matrix metalloproteinase** is also **membrane** bound. When lung cell **membrane** fractions were probed in immunoblots with polyclonal antibodies against a recombinant fragment of the 669-amino-acid chain, a protein of M(r) 72,000 reacted preferentially with the antibodies. Northern-blot analysis demonstrated quite different tissue distributions of mRNA for the two **membrane**-type **matrix metalloproteinases**. While mRNA for the 582-amino-acid enzyme was found predominantly in lung, placenta, kidney, ovary, intestine, prostate and spleen, mRNA for the 669-amino-acid enzyme appeared to be synthesized preferentially in liver, placenta, testis, colon and intestine. Substantial amounts of the latter mRNA were also detected in pancreas, kidney, lung, heart and skeletal muscle.

L80 ANSWER 5 OF 18 MEDLINE DUPLICATE 4

L80 ANSWER 6 OF 18 Elsevier BIOBASE COPYRIGHT 2002 Elsevier Science B.V. DUPLICATE

L80 ANSWER 7 OF 18 MEDLINE DUPLICATE 6

AB Matrix metalloproteinases (MMPs) play key roles in tissue remodeling during physiological and pathological processes by degrading various extracellular matrix (ECM) components. Although nine distinct MMPs have been characterized by cDNA cloning, there are thought to be more corresponding to the complexity of the ECM. MMP genes expressed in human tissues and cell lines were analyzed by the polymerase chain reaction (PCR) using degenerate primers that corresponded to the conserved amino acid (aa) sequences of the MMPs. One isolated complementary DNA (cDNA) fragment had sequence homology to the reported MMPs, but was otherwise unique. A human placenta cDNA library (Clontech) was screened using the fragment as a probe and a 3.4-kb cDNA fragment containing a long open reading frame (potentially encoding 582 aa) was isolated. The putative gene product had a common domain structure and the conserved sequence of a MMP, but it had a unique transmembrane (TM)-like structure at the C terminus. It should, therefore, be an TM protein, whereas all the other reported MMPs are secretory proteins. Thus, the gene is thought to be the first of a new subclass of MMPs whose products are potentially expressed on the cell surface.

L80 ANSWER 8 OF 18 HCAPLUS COPYRIGHT 2002 ACS

AB The authors examd. the common signal transduction mechanisms governing collagenase (MMP-1), stromelysin-1 (MMP-3), and tissue inhibitor of metalloproteases (TIMP-1) gene expression in human synovial fibroblasts for insight into the pathophysiol. of arthritis. MMP-1, MMP-3, and TIMP-1 expression and synthesis were induced in cultured human synoviocytes with recombinant human interleukin 1.beta. in the absence or presence of either chem. inhibitors of protein kinase A and C (PKA, PKC), or prostaglandin E2, or cAMP mimetics. The authors used enzyme immunoassays (EIA) to det. MMP-1, MMP-3, and TIMP-1 antigen levels in spent culture medium and Northern hybridization to measure steady state mRNA expression levels. Extracellular signals (e.g., IL-1, phorbol myristic acetate) that result in the activation of cytoplasmic PKC augment in tandem the expression and synthesis of MMP-1, MMP-3, and TIMP-1 in human synovial fibroblasts. In

addn., such signals induce nuclear transcription factors (e.g., activator protein 1) that bind to common gene regulatory elements and augment promoter activity of MMP-1, MMP-3, and TIMP-1 gene promoter constructs. In contrast, signals that activate PKA oppose PKC mediated signals, in that the expression of MMP-1, MMP-3, and TIMP-1 are suppressed. Exptl. data suggest that the expression of MMP-1, MMP-3, and TIMP-1 are coordinated through a series of common cytoplasmic signal transducing pathways, cis-regulatory elements, and nuclear transacting factors.

L80 ANSWER 9 OF 18 HCAPLUS COPYRIGHT 2002 ACS

AB Matrix metalloproteinases (MMP) are important enzymes responsible for the dissoln. of extracellular matrix (ECM) structure during tumor invasion and metastasis. There are nine known MMP that are encoded by different genes. However, the complexity of the ECM components suggests that there are more MMP involved in the efficient turn-over of ECM. In addn., a membrane-bound MMP is postulated as an activator for inactive latent MMP-2. Thus, to identify such new MMP genes, cDNA were prepd. from various sources and MMP gene fragments were amplified by reverse transcribed-PCR (RT-PCR) with degenerate oligo primers corresponding to the highly conserved amino acid residues among MMP family. Fragments were subcloned into a plasmid vector and nucleotide sequences of 168 clones analyzed. One hundred twelve clones were of the known MMP genes and 5 clones were cDNA fragments of a new MMP gene, which were homologous with the MMP genes. A 3.4 k base (bp) cDNA was obtained from human placenta cDNA library by screening with this cDNA fragment as a probe. A long open reading frame that potentially encodes 582 amino acids was identified. The deduced gene product had similar domain structures to the known MMP and a unique 24 hydrophobic amino acids stretch (transmembrane domain), which is sufficient to pass through the plasma membrane, at the carboxyl terminus. This predicted transmembrane domain at the carboxyl terminus does not exist in other MMP. Thus, we call this product membrane type-MMP (MT-MMP). The product of MT-MMP gene was detected as a 63 kDa protein from cells transfected with MT-MMP plasmid. Actually, immunostaining of the cells transfected with Mt-MMP plasmid using anti-MT-MMP antibody revealed that MT-MMP expressed on the cell surface. Working on the knowledge that the expression of MT-MMP on the cell surface consisted with the activator of latent MMP-2 described previously, we investigated the function of MT-MMP as such an activator. Expression of MT-MMP results in conversion a latent MMP-2 (66 kDa) to an active form (62 kDa) through an intermediate form (64 kDa). These results suggested that MT-MMP is the activator for latent MMP-2.

L80 ANSWER 10 OF 18 HCAPLUS COPYRIGHT 2002 ACS

AB It is widely accepted that a major role of **matrix metalloproteinases** in the metastatic process is degrdn. of basement **membrane** during cancer cell invasion. The authors tested the hypothesis that the redn. in metastatic potential which has been demonstrated for B16F10 melanoma cells genetically engineered to overexpress tissue inhibitor of metalloproteinase-1 (TIMP-1) is caused by a decrease in their ability to extravasate. Using intravital videomicroscopy of chick embryo chorioallantoic membrane, the authors studied extravasation of B16F10 cells and B16F10 cells transfected to overexpress TIMP-1. More than 800 cells in 36 chick embryos were analyzed for each cell line during 72 h postinjection. TIMP-1 upregulation had no effect on the time course of extravasation, virtually all cells from both cell lines having extravasated by 36 h. The authors also studied the morphol. of micrometastases at day 3 and redn. in size and no. of tumors at day 7 were obsd. for TIMP-1 overexpressor cells compared to B16F10. The authors findings illustrate that the imbalance between TIMP and metalloproteinases created by overexpression of TIMP-1 in B16F10 cells reduces their metastatic ability in vivo by affecting tumor growth postextravasation.

L80 ANSWER 11 OF 18 MEDLINE DUPLICATE 7

AB One critical event of tumour invasion that signals the initiation of the metastatic cascade is thought to be interaction of the tumour cell with the basement membrane. Basement membranes may also pose as barriers to tumour cell invasion at multiple points later in the metastatic cascade, including during the processes of vascular infiltration and extravasation. Thus, an important proteolytic event in the metastatic cascade, and also angiogenesis, appears to be degradation of basement **membrane** components. A specific class of extracellular **matrix** degrading metalloenzymes, the **matrix metalloproteases**, and their endogenous inhibitors, the tissue inhibitors of metalloproteases, are thought to have a role in the creation of the proteolytic defect in basement membrane type IV collagen. We will review the evidence which indicates that matrix metalloproteases and tissue inhibitors of metalloproteases are essential for tumour cell invasion and angiogenesis. The regulation of **matrix metalloproteases** will be discussed, including **gene** activation and transcription, messenger ribonucleic acid (mRNA) stability, binding of proenzymes to cell membranes and/or matrix components, proenzyme activation, and inactivation by endogenous inhibitors. We will also discuss the mechanism for tissue inhibitor of metalloproteases-mediated inhibition of tumour invasion and angiogenesis. This appears, at least in part, to be through inhibition of protease activity required for cellular invasion, although recent observations suggest that tissue inhibitors of metalloproteases affect other distinct groups of biological activities through mechanisms other than matrix metalloprotease inhibition.

L80 ANSWER 12 OF 18 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

L80 ANSWER 13 OF 18 MEDLINE DUPLICATE 8
AB Gelatinase A (type-IV collagenase; M(r) 72,000) is produced by tumour stroma cells and is believed to be crucial for their invasion and metastasis, acting by degrading extracellular matrix macro-molecules such as type IV collagen. An inactive precursor of gelatinase A (pro-gelatinase A) is secreted and activated in invasive tumour tissue as a result of proteolysis which is mediated by a fraction of tumour cell membrane that is sensitive to metalloproteinase inhibitors. Here we report the cloning of the complementary DNA encoding a new **matrix metalloproteinase** with a potential **transmembrane** domain. Expression of the **gene** product on the cell surface induces specific activation of pro-gelatinase A in vitro and enhances cellular invasion of the reconstituted basement membrane. Tumour cells of invasive lung carcinomas, which contain activated forms of gelatinase A, were found to express the transcript and the gene product. The new metalloproteinase may thus trigger invasion by tumour cells by activating pro-gelatinase A on the tumour cell surface.

L80 ANSWER 14 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AB In an effort to understand the mechanism of matrix metalloproteinase (MMP) induction, lapine synoviocytes were isolated and incubated with phorbol myristate acetate (PMA) and autocrine "cell-activating factors" (CAF), agents which significantly increase MMP mRNA abundance. AP-1 complexes, formed by c-fos and c-jun which bind to 5' residues of the MMP genes, seem causally related to MMP gene expression in response to PMA. However, although AP-1 DNA binding activity is strongly induced following exposure of synoviocytes to CAF, MMP gene expression in response to CAF does not correlate well with AP-1 activity and is not inhibited by antisense DNA to fos and jun. The authors hypothesize that there is a CAF-response factor involved in MMP gene expression and that this factor competes with the binding of the AP-1 complex to its target response element.

L80 ANSWER 15 OF 18 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AB The human stromelysin 3 (STMY3) **gene**, a new **membrane** of the **matrix metalloproteinase** (MMP) **gene** family, may contribute to breast cancer cell invasion, and has been

localized by in situ hybridization to the long arm of chromosome 22. As demonstrated using a panel of somatic cell hybrids, the STMY3 gene is in band 22q11.2, in close proximity to the BCR gene involved in chronic myeloid leukemia, but far from the (11;22) translocation breakpoint observed in Ewing sarcoma. This position differs from that reported on chromosomes 11 and 16 for the other MMP genes, suggesting that stromelysin 3 could be a member of a new MMP subfamily.

L80 ANSWER 16 OF 18 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AB Secretion of glomerular cell-derived matrix metalloproteinases (MMPs) and their specific inhibitors, TIMP-1,2 may play an important role in the turnover of the glomerular extracellular matrix under basal and pathologic conditions. A 66-68 kd MMP secreted by cultured mesangial cells (MC) with activity against Type IV collagen and gelatin was purified and shown by amino-acid sequence analysis to be identical with a Type IV collagenase/gelatinase secreted by certain transformed tumor cell lines. The expression of the mesangial MMP in vivo was limited within the kidney to a small subset of the intrinsic glomerular mesangial cell population. After induction of acute anti-Thy 1.1 glomerulonephritis, there was a large increment in the number of Type IV collagenase-secreting MC, temporally coincident with the development of mesangial hypercellularity. The expression of the MMP inhibitor protein, TIMP-1, was not changed over this period. Ultrastructural studies localized the mesangial MMP to areas of evolving mesangiolysis and at sites of glomerular basement membrane disruption. Enhanced expression of the mesangial cell-derived Type IV collagenase may contribute to the evolution of glomerular injury in this model of immune complex-mediated glomerulonephritis or may be involved in the extensive matrix remodeling process that accompanies this form of glomerular injury.

L80 ANSWER 17 OF 18 HCAPLUS COPYRIGHT 2002 ACS
AB Human rheumatoid synovial cells in culture secrete at least three related metalloproteinases that digest extracellular matrix macromols. One of them, termed matrix metalloproteinase 2 (MMP-2), has been purified as an inactive zymogen (proMMP-2). The final product is homogeneous on SDS PAGE with Mr 72,000 under reducing conditions. The N-terminal sequence of proMMP-2 is Ala-Pro-Ser-Pro-Ile-Ile-Lys-Phe-Pro-Gly-Asp-Val-Ala-Pro-Lys-Thr, which is identical to that of the 72-kDa type IV collagenase/gelatinase. The zymogen can be rapidly activated by 4-aminophenylmercuric acetate to an active form of MMP-2 with Mr 67,000, and the new N-terminal generated is Tyr-Asn-Phe-Phe-Pro-Arg-Lys-Pro-Lys-Trp-Asp-Lys-Asn-Gln-Ile. However, following 4-aminophenylmercuric acetate activation, MMP-2 is gradually inactivated by autolysis. Nine endopeptidases (trypsin, chymotrypsin, plasmin, plasma kallikrein, thrombin, neutrophil elastase, cathepsin G, matrix metalloproteinase 3, and thermolysin) were tested for their abilities to activate proMMP-2, but none had this ability. This contrasts with the proteolytic activation of proMMP-1 (procollagenase) and proMMP-3 (prostromelysin). The optimal activity of MMP-2 against azocoll is around pH 8.5, but about 50% of activity is retained at pH 6.5. Enzymic activity is inhibited by EDTA, 1,10-phenanthroline or tissue inhibitor of metalloproteinases, but not by inhibitors of serine, cysteine, or aspartic proteinases. MMP-2 digests gelatin, fibronectin, laminin, and collagen type V, and to a lesser extent type IV collagen, cartilage proteoglycan and elastin. Comparative studies on digestion of collagen types IV and V by MMP-2 and MMP-3 (stromelysin) indicate that MMP-3 degrades type IV collagen more readily than MMP-2, while MMP-2 digests type V collagen effectively. Biosynthetic studies of MMPs using cultured human rheumatoid synovial fibroblasts indicated that the prodn. of both proMMP-1 and proMMP-3 is negligible but it is greatly enhanced by the treatment with rabbit-macrophage-conditioned medium, whereas the synthesis of proMMP-2 is constitutively expressed by these cells and is not significantly affected by the treatment. This suggests that the physiol. and/or pathol. role of MMP-2 and its site of action may be different from those of MMP-1 and MMP-3.

L80 ANSWER 18 OF 18 HCAPLUS COPYRIGHT 2002 ACS

AB Collagenolytic activity in the culture medium of human rheumatoid synovial cells was not detectable but full activity was detected after treatment with 1 mM 4-aminophenylmercuric acetate (APMA). When pro-matrix metalloproteinase 3 (proMMP-3) was removed from the culture medium, only partial activation by trypsin or APMA was obsd. Full activation was achieved when proMMP-3 was added back to the culture medium. MMP-3 (also called stromelysin) cleaved the Gln80-Phe81 bond of procollagenase. This was greatly accelerated when a portion of the propeptide was removed by the action of proteinases or APMA. Thus, MMP-3 is an endogenous activator of procollagenase.

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